Annihilating Cancer Cells at a Minimal Cost for a Model with Delay

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Abstract

In this paper, we look at a model depicting the relationship of cancer cells in different development stages with immune cells and a cell cycle specific chemotherapy drug. The model includes a constant delay in the mitotic phase. By applying the optimal control theory, we seek to minimize the cost associated with the chemotherapy drug and look at minimizing the tumor cells.Global existence of a solution has been shown for this model and existence of an optimal control has also been proven. Optimality conditions and characterization of the control is discussed.

1 Introduction

Cells that can not regulate their own growth and division are classified as cancerous. Cancer cells that don't match the growth of normal tissue create an abnormal mass of tissue referred to as tumors. Lu *et. al* [9] paper took a more extensive look at the development of cancer cells by noting the three phases through which they travel. These stages are the mitotic-phase (dividing), quiescent phase (resting), and the interphase. The body's main defenses against tumors are the white blood cells, often called lymphocytes, generated by the immune system. Benign type tumor can be contained or it can grow into surrounding tissue. Tumors that grow into and destroy surrounding tissue are referred to as malignant. When either type of tumor begins to grow, it is common for them to be surgically removed and/or treated with chemotherapy.

Chemotherapy is the administering of anti-cancer drugs [2]. Numerous variables, such as toxicity, cause treatment to be highly complex. This complexity causes the strategy of treatment to vary widely from person to person. Immunotherapy is also another way to fight cancer. This type of treatment is a process of boosting the immune system in specific areas which target cancer cells and leave healthy cells relatively untouched. While both treatments are usually used separately, Kirschner and Panetta [8] investigate the biological perspective of a combination therapy approach. This research has sparked interest in theoretical exploration using mathematical modeling.

It can be quite useful to use mathematical modeling when determining strategies for fighting diseases which will enhance the quality of life for the patients. By using updated mathematical models, it is possible to make quantitative and testable predictions about real life patients. This enables a more accurate approach to treatments [10]. Fletcher[5], author of a text on practical methods of optimization described optimization as finding the 'best' solution to a mathematical problem. Fletcher's book describes the behavior of many methods for solving optimal control problems. Part of these methods include finding the optimal criteria and most efficient strategy needed for specific results to be found [5].

Optimal control dates back to the 1950's and has often been applied to cancer therapy strategies. A study from 2000 uses optimal control techniques in designing drug protocols that will kill a desired amount of tumor cells without killing the host.[1] Works by Kim *et. al* [7], Swan and Vincent [12], and Murray [11] have successfully applied optimal control to maximize the effects of the chemotherapy drug while minimizing the toxicity and damage done by the drug. For this model and paper, we will find the optimal strategy for minimizing the number of cancer cells and amount of chemotherapy drug needed. Ideally, we want to eliminate all the cancer cells and do as little damage to the body as possible.

A recent study by Lu *et. al* [9] looks at the stability of a mitotic phase-specific drug and its interaction with the immune system and cancer cells, whose results show a significant decrease in the number of cancer cells but no change in the stability. Another study by Villasana and Radunskaya [13] also considered the stability of using a cycle-specific drug and found that the stability depended on a delay of the cells moving from the interphase to mitosis. It is important to note that [13] didn't look at the quiescent phase; whereas, [9] found that this phase greatly influences the cancer as a whole. The nondimensionalized model in [9] is the model this paper will use to conduct further study using optimal control techniques.

The arrangement of this paper starts with describing the model being used in Section 2. Section 3.1 gives context to the objective functional and establishes the existence of a solution to our problem given an optimal control in the admissible control set. Characterization of the controls is located in 3.4, while section 4 is the numerical solutions.

2 Model

The cell cycle is split up into 3 phases; the quiescent phase where cells rest, the interphase where cells prepare for mitosis, and then the mitotic phase where cells divide. Lu *et. al* [9] develops the interaction between cells and the three phases, the immune system, and the cycle- specific drug. The variables used are as follows:

- x- number of cancer cells in interphase phase
- y- number of cancer cells in mitotic phase
- z- number of cancer cells in the quiescent phase

- I- number of lymphocytes
- u- biomass of chemotherapy drug

The model is:

$$\frac{dx}{dt} = s\,\alpha_3\,z(t) - \alpha_1 x(t) - (\sigma_1 + k_1 I(t))\,x(t) \tag{1}$$

$$\frac{dy}{dt} = \alpha_1 x(t-\tau) - (\alpha_2 + \sigma_2 + k_2 I(t))y(t) - k_4(1 - (e^{-k_5 u(t)})y(t) \tag{2}$$

$$\frac{dz}{dt} = 2s^{-1}\alpha_2 y(t) - (\alpha_3 + \sigma_3 + k_3 I(t))z(t) \tag{3}$$

$$\frac{dI}{dt} = k + \left(\frac{\rho I(t)(x+y+sz)^n}{a + (x+y+sz)^n}\right) - (\sigma_4 + c_1 x(t) + c_2 y(t) + c_3 z(t))\; I(t) \tag{4}$$

$$- k_6(1 - e^{-k_7 u(t)})I(t) \tag{5}$$

$$\frac{du}{dt} = -\gamma u(t) + v(t) \tag{6}$$

$$\tag{7}$$

where the initial conditions are

$$x(t) = \phi_1,\ t \in [-\tau, 0],\ y(0) = y_0,\ z(0) = z_0,\ I(0) = I_0,\ u(0) = u_0 \tag{8}$$

It is important to note that all the constants are positive and that the mitotic phase is the only one with a delay present. The terms $\alpha_1, \alpha_2, \alpha_3$ describe the rate at which cells travel from each phase. The natural death rate of cells have parameters denoted by $\sigma_1, \sigma_2, \sigma_3$, while the death rate parameters by the immune cells are given as c_1, c_2, c_3. The term $\frac{\rho I(t)(x+y+sz)^n}{a+(x+y+sz)^n}$ is the nonlinear growth of the immune system [13]. Destruction by drugs is shown by $(1 - (e^{-k_5 u(t)})$ and $(1 - e^{-k_7 u(t)})$ [13]. We assume that once the chemotherapy drug is given, it has an exponential decay rate of $-\gamma$. We also assume that $u_0 > 1$.

3 Quadratic Control

3.1 Objective Functional

There will be two objective functionals, one without salvage terms and the other with salvage terms. We seek to minimize the first objective functional

$$J_1(v) = \int_0^{t_f} [\frac{\epsilon}{2} v^2(t) + x(t) + y(t) + sz(t)]dt \tag{9}$$

over the set $\mathbb{V} = \{t \in [0, t_f]|\ 0 \leq v(t) \leq 1\}$. Here ϵ is a weight factor, representing the cost to the system and x, y, z are the cancer cells. So we are minimizing both

the tumor cells and the cost associated with the chemotherapy drug. We will also minimize the second objective functional

$$J_2(v) = \int_0^{t_f} \frac{\epsilon}{2} v^2(t)dt + [x(t_f) + y(t_f) + sz(t_f)] \tag{10}$$

over the same set and with the same weight factor ϵ. The cost associated with drug is being minimized, but the cancer cells x, y, and z are minimized at the final time.

3.2 Existence

We establish the existence of a solution to the delay differential system using results from R.D. Driver's text [4]. For notational purposes, we use

$$f(\overrightarrow{x}) = \begin{pmatrix} s\alpha_3\, z(t) - \alpha_1 x(t) - (\alpha_1 + k_1 I(t))\, x(t) \\ \alpha_1 x(t-\tau) - (\alpha_2 + \sigma_2 + k_2 I(t))y(t) - k_4(1 - (e^{(-k_5 u(t))}y(t))) \\ 2s^{-1}\alpha_2 y(t) - (\alpha_3 + \sigma_3 + k_3 I(t))z(t) \\ k + \left(\frac{\rho I(t)(x+y+sz)^n}{a+(x+y+sz)^n}\right) - (\sigma_4 + c_1 x(t) + c_2 y(t) + c_3 z(t))\, I(t) \qquad -k_6(1 - e^{-k_7 u(t)})I(t) \\ -\gamma u(t) \end{pmatrix}$$

We will use a lemma from [4] that will help establish existence on a smaller interval, which will aide in the quest for existence on the whole interval.

Theorem 3.1. *[4] If $f(\overrightarrow{x}) : [0, t_f)$ has continuous first partial derivatives with respect to all but its first argument, then $f(\overrightarrow{x})$ is locally Lipschiztian.*

Proof. The partial of $f(\overrightarrow{x})$ with respect to its first argument is

$$\begin{pmatrix} -\alpha_1 - \sigma_1 - k_1 I(t) & 0 & s\alpha_3 & 0 & 0 \\ \alpha_1 & -(\alpha_2 + \sigma_2 + k_2 I(t)) - k_4(1 - e^{-k_5 u(t)}) & 0 & 0 & 0 \\ 0 & 2s^{-1}\alpha_2 & -(\alpha_3 + \sigma_3 + k_3 I(t)) & 0 & 0 \\ \frac{I(t)\rho n(x+Y+sz)^{n-1}}{(a+(x+y+sz)^n)^2} - C_1 & \frac{I(t)\rho n(x+Y+sz)^{n-1}}{(a+(x+y+sz)^n)^2} - C_2 & \frac{I(t)\rho n s(x+Y+sz)^{n-1}}{(a+s(x+y+sz)^n)^2} - C_3 & I(t) - k_6(1 - e^{-k_7 u(t)}) & 0 \\ 0 & 0 & 0 & 0 & -\gamma \end{pmatrix}$$

Since $a, x, y, z > 0$, then all the partials are continuous. Thus $f(\overrightarrow{x})$ is locally Lipschitzian on $[-\tau, t_f - \tau)$. □

We then provide the following transformation:
$F(t, x_t(-\tau), y(t), z(t), I(t), u(t)) \equiv f(t, x(t-\tau), y(t), z(t), I(t), u(t))$

By using example 6 and theorem 3.1 from Driver [4], we can now say that F is locally Lipschitzian on $[-\tau, t_f - \tau)$. Also $F(t, x_t, y, z, I, u)$ is continuous with respect to t in $[-\tau, t_f - \tau)$ which satisfies the Continuity Condition located in the Appendix. Thus since $F(t, x_t, y, z, I, u)$ is locally Lipschitzian and is continuous, then $F(t, x_t, y, z, I, u)$

gives existence and a unique solution on $[-\tau, t_f - \tau)$.
Now that existence and uniqueness has been proved for the interval $[-\tau, t_f - \tau)$, we need to use another theorem from Driver [4] to prove existence and uniqueness on the entire interval.

Theorem 3.2. *Global Existence: Let $F(t, x, y_t, z, I, u)$ satisfy the continuity condition and be locally Lipschiztian on $[-\tau, t_f - \tau)$. Assume further that $||F(t, \psi)|| \leq M(t) + N(t)||\psi||$ where M(t) and N(t) are continuous functions and $\psi = (x_t, y, z, I, u)^T$ then the unique noncontinuable solution exists on the entire interval $[0, t_f)$.*

Proof. $F(t, x_t, y, z, I, u)$ has already been shown to be locally Lipschitzian and to satisfy the continuity condition, so we just need to show $||F(t, \psi)|| \leq M(t)+N(t)||\psi||$ on $[0, t_f)$.
We recognize physically that $x > 0, y > 0, z > 0$, and we consider supersolutions of $x(t)$, $y(t)$, $z(t)$ as $X_{max}, Y_{max}, Z_{max}$ respectively. With performing separation of variables on the differential equation (5), we find the solution for u which is $u(t) = (u_0 - 1)e^{-\gamma t} \leq u_0$. With this replacement the set of supersolutions become

$$\begin{pmatrix} X \\ Y \\ Z \\ I \end{pmatrix}' = \begin{pmatrix} 0 & 0 & s\alpha_3 & 0 \\ \alpha_1 & k_4 e^{-k_5 u_0} & 0 & 0 \\ 0 & 2s^{-1}\alpha_2 & 0 & 0 \\ 0 & 0 & \rho + k_6 e^{-k_7 u_0} & 0 \end{pmatrix} \begin{pmatrix} X \\ Y \\ Z \\ I \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ 0 \\ k \end{pmatrix}$$

Note that the matrix doesn't include the growth due to stimulus term because

$$\frac{(x + y + sz)^n}{(a + (x + y + sz)^n)} = \frac{w}{a + w} \leq 1 \; if \; w = (x + y + sz)^n$$

We have that $||F(t, \psi)|| \leq M+N||\psi||$ where $M = \begin{pmatrix} 0 \\ 0 \\ 0 \\ k \end{pmatrix}$ and $N = \begin{pmatrix} 0 & 0 & s\alpha_3 & 0 \\ \alpha_1 & k_4 e^{-k_5 u_0} & 0 & 0 \\ 0 & 2s^{-1}\alpha_2 & 0 & 0 \\ 0 & 0 & \rho + k_6 e^{-k_7 u_0} & 0 \end{pmatrix}$.
Thus, $F(t, \psi)$ has global existence on $[0, t_f)$. □

3.3 Existence of an Optimal Control

Theorem 3.3. *There exists an optimal control in our admissible control set, $\mathbb{V}$ for $J_2(v)$.*

The theorem we used to prove the existence of an optimal control is located in the appendix. A similar analysis follows for $J_1(v)$.

Proof. First we must note that the assumptions A_1 through A_3, for formulating an optimal control problem, are met because our problem is defined and continuous for all variables. It has also been shown that $f(t, x_t, y, z, I, u, v(t))$ is bounded above in the proof of existence of a solution to our problem. Since these assumptions are met, then we must show each of the remaining parts of the theorem in the appendix to properly

prove the existence of an optimal control in $\mathbb{V}$ that minimizes the functional $J_i(v)$ for $i = 1, 2$. As stated above, the assumptions A_1 through A_3 have been met. Since the initial conditions are all constants then the fixed initial function $\phi\epsilon([\alpha, t_0], S)$. In addition, since our solution is bounded and exists along with our control then a target set is nonempty and upper semicontinuous. Also, our control being bounded, provides us with the change in our control being bounded by a constant. We note that there exists a minimizing sequence $v^n \, \epsilon \, \mathbb{V}$ such that

$$\lim_{n\to\infty} J_2(v^n) = \inf_{v\,\epsilon\mathbb{V}} J(v) \tag{11}$$

Since we know there exists a solution to our problem equations $(1-5)$, we define $x^n = x(v^n)$, $y^n = y(v^n)$,$z^n = z(v^n)$. Also, this solution set is bounded on R^n. We see that $x^n(t_f) \to x^*(t_f)$, $y^n(t_f) \to y^*(t_f)$, and $z^n(t_f) \to z^*(t_f)$. Moreover, we have that $v^n \rightharpoonup v^*$ in $Ł^2(0, t_f)$ since v^n is in $\mathbb{V}$. We must analyze $\lim_{n\to\infty} \inf J_2(v^n) = \liminf_{n\to\infty}[\int_0^{t_f} \frac{\epsilon}{2}(v^n)^2\, dt \; + \; (x^n(t_f) + y^n(t_f) + sz^n(t_f))]$

By Fatou's Lemma,

$$\liminf_{n\to\infty} J_2(v^n) \geq \int_0^{t_f} \frac{\epsilon}{2} \liminf_{n\to\infty} [v^n]^2\, dt \; + \; (x^* + y^* + sz^*) \tag{12}$$

$$\geq \int_0^{t_f} \frac{\epsilon}{2}(v^*)\, dt \; + \; (x^* + y^* + sz^*) \tag{13}$$

So

$$\liminf_{n\to\infty} J(v^n) \leq \lim_{n\to\infty} J(v^n) \leq J(v) \tag{14}$$

Thus $J(v^*) \leq J(v)$ with $\mathbb{V}$ being nonempty.

All five properties are fulfilled from Das and Sharma's theorem, thus there is an optimal control in $\mathbb{V}$. □

3.4 Characterization of the Controls

Theorem 3.4 (Characterization of the Optimal Control)**.** *Given an optimal control, $v^*(t)$, and solutions of the corresponding state system, there exist adjoint variables λ_i for $i = 1, 2, ...5$ satisfying the following:*

For $J_1(v)$ we have

$$-\frac{\partial H}{\partial x_t} - \frac{\partial H}{\partial x_{t-\tau}} = \lambda_1' = -1 + \lambda_1(\alpha_1 + \sigma_1) + \lambda_1 k_1 I - \lambda_4 \frac{\rho I n a (x + y + sz)^n}{(a + (x + y + sz)^n)^2} + \lambda_4 c_1 - \lambda_2 \alpha_2|_{t+\tau}$$

$$for 0 \leq t \leq t_f - \tau$$

$$-\frac{\partial H}{\partial x_t} = \lambda_1' = \lambda_1(\alpha_1 + \sigma_1) + \lambda_1 k_1 I - \lambda_4 \frac{\rho I n a (x + y + sz)^n}{(a + (x + y + sz)^n)^2} + \lambda_4 c_1$$

$$for t_f - \tau \leq t \leq t_f$$

$$\begin{aligned}
-\frac{\partial H}{\partial y} = \lambda_2' =& -1 + \lambda_2 k_2 I + \lambda_2 k_4 (1 - e^{-k_5 u}) + \lambda_2(\alpha_2 + \sigma_2) - \lambda_3(2s^{-1}\alpha_2) \\
& - \lambda_4\Big(\Big(\frac{a\rho I(t) n (x + y + sz)^{(n-1)}}{(a + (x + y + sz)^n)^2}\Big) - c_2\Big) \\
-\frac{\partial H}{\partial z} = \lambda_3' =& -s - \lambda_1 s\alpha_3 + \lambda_3 I(t) k_3 - \lambda_4\Big(\frac{a\rho I(t) nas (x + y + sz)^{(n-1)}}{(a + (x + y + sz)^n)^2}\Big) \\
& - \lambda_4 c_3 I(t) \\
-\frac{\partial H}{\partial I} = \lambda_4' =& \lambda_1 k_1 x + \lambda_2 k_2 y - \lambda_4\Big(\Big(\frac{\rho (x + y + sz)^n}{a + (x + y + sz)^n} + c_3 z + k_6 e^{-k_7 u}\Big)\Big) \\
& + \lambda_3 k_3 z \\
-\frac{\partial H}{\partial u} = \lambda_5' =& \lambda_2 k_4 k_5 e^{-k_5 u(t)} + \lambda_4 k_6 k_7 e^{-k_7 u(t)} + \lambda_5 \gamma
\end{aligned}$$

with $\lambda_i(t_f) = 0$ *for* $i = 1, 2, ..5$
and associated with $J_2(v)$ *we have*

$$\begin{aligned}
-\frac{\partial H}{\partial x_t} - \frac{\partial H}{\partial x_{t-\tau}} = \lambda_1' =& \lambda_1(\alpha_1 + \sigma_1) + \lambda_1 k_1 I - \lambda_4 \frac{\rho I n a (x + y + sz)^{n-1}}{(a + (x + y + sz)^n)^2} \\
& + \lambda_4 c_1 - \lambda_2 \alpha_2|_{t+\tau}
\end{aligned}$$

$$for\ 0 \leq t \leq t_f - \tau$$

$$\begin{aligned}
-\frac{\partial H}{\partial x_t} = \lambda_1' =& \lambda_1(\alpha_1 + \sigma_1) + \lambda_1 k_1 I - \lambda_4 \frac{\rho I n a (x + y + sz)^{n-1}}{(a + (x + y + sz)^n)^2} \\
& + \lambda_4 c_1
\end{aligned}$$

$$for\ t_f - \tau \leq t \leq t_f$$

$$\begin{aligned}
-\frac{\partial H}{\partial y} = \lambda_2' =& \lambda_2 k_2 I + \lambda_2((\alpha_2 + \sigma_2) + \lambda_2 k_4 (1 - e^{-k_5 u}) - \lambda_3(2s^{-1}\alpha_2) \\
& - \lambda_4\Big(\Big(\frac{a\rho I(t) n (x + y + sz)^{(n-1)}}{(a + (x + y + sz)^n)^2}\Big) - c_2\Big) \\
-\frac{\partial H}{\partial z} = \lambda_3' =& -\lambda_1 s\alpha_3 + \lambda_3(\alpha_3 + \sigma_3) + \lambda_3 I(t) k_3 - \lambda_4\Big(\frac{a\rho I(t) nas (x + y + sz)^{(n-1)}}{(a + (x + y + sz)^n)^2}\Big) \\
& - \lambda_4 I(t) \\
-\frac{\partial H}{\partial I} = \lambda_4' =& \lambda_1 k_1 x + \lambda_2 k_2 y + \lambda_3 k_3 z - \lambda_4\Big(\Big(\frac{\rho (x + y + sz)^n}{a + (x + y + sz)^n}\Big) - k_6 k_7 e^{-k_7 u(t)}\Big) \\
-\frac{\partial H}{\partial u} = \lambda_5' =& \lambda_2 k_4 k_5 e^{-k_5 u(t)} + \lambda_4 k_6 k_7 e^{-k_7 u(t)} + \lambda_5 \gamma
\end{aligned}$$

with

$$\lambda_1(t_f) = 1 \tag{15}$$
$$\lambda_2(t_f) = 1 \tag{16}$$
$$\lambda_3(t_f) = 1 \tag{17}$$
$$\lambda_4(t_f) = 0 \tag{18}$$
$$\lambda_5(t_f) = 0 \tag{19}$$

Furthermore, $v^*(t)$ can be represented by

$$v^* = \min\left(\max\left(0, \frac{-\lambda_5}{\epsilon}\right), 1\right)$$

Proof. We begin by forming the Lagrangian. Since $0 \leq v \leq 1$, the controls are bounded; thus, the Lagrangian takes the following form:

$$\mathcal{L} = H - W_1(t)v(t) - W_2(t)(1 - v(t)),$$

where H_i is the Hamiltonian associated with $J_i(v)$ for $i = 1, 2$.

$$\begin{aligned}
H_1 =& x(t) + y(t) + sz(t) + \frac{\epsilon}{2}v^2(t) \\
&+ \lambda_1[(-(\alpha_1 + \sigma_1)x(t) + s\alpha_3 z(t) - k_1 x(t)I(t))] \\
&+ \lambda_2[(\alpha_1 x(t-\tau) - (\alpha_2 + \sigma_2)y(t) - k_2 y(t)I(t) - k_4(1 - e^{-k_5 u(t)})y(t))] \\
&+ \lambda_3[2s^{-1}\alpha_2 y(t) - (\alpha_3 + \sigma_3)z(t) - k_3 z(t)I(t)] \\
&+ \lambda_4[k + \frac{\rho I(t)(x + y + sz)^n}{(a + (x + y + sz)^n)} - (\sigma_4 + c_1 x(t) + c_2 y(t) + c_3 z(t)I(t) - k_6(1 - e^{-k_7 u(t)})I(t))] \\
&+ \lambda_5[-\gamma u(t) + v(t)]
\end{aligned}$$

for $J(v_1)$ and

$$\begin{aligned}
H_2 =& \frac{\epsilon}{2}v^2(t) \\
&+ \lambda_1[(-(\alpha_1 + \sigma_1)x(t) + s\alpha_3 z(t) - k_1 x(t)I(t))] \\
&+ \lambda_2[(\alpha_1 x(t-\tau) - (\alpha_2 + \sigma_2)y(t) - k_2 y(t)I(t) - k_4(1 - e^{-k_5 u(t)})y(t))] \\
&+ \lambda_3[2s^{-1}\alpha_2 y(t) - (\alpha_3 + \sigma_3)z(t) - k_3 z(t)I(t)] \\
&+ \lambda_4[k + \frac{\rho I(t)(x + y + sz)^n}{(a + (x + y + sz)^n)} - (\sigma_4 + c_1 x(t) + c_2 y(t) + c_3 z(t)I(t) - k_6(1 - e^{-k_7 u(t)})I(t))] \\
&+ \lambda_5[-\gamma u(t) + v(t)]
\end{aligned}$$

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and $W_i(t) \geq 0$ are penalty multipliers such that

$$\left.\begin{aligned} W_1(t)v(t) &= 0 \\ W_2(t)(1 - v(t)) &= 0 \end{aligned}\right\} \text{ at } v^*(t)$$

Although the Hamiltonians are slightly different, both objective functionals will have the same control characterizations. Using Kamien and Schwartz[6] in conjunction with Pontryagin's Maximum Principle, we obtain the adjoint differential equations and the terminal conditions. To find the representation for $v(t)$, we analyze the necessary condition for optimality $\frac{\partial \mathcal{L}}{\partial v} = 0$,

$$\frac{\partial \mathcal{L}}{\partial v} = \frac{\partial H_i}{\partial v} - W_1 + W_2 = 0.$$

To determine an explicit expression for v, we consider three cases:

1. Consider the set $\{\mathrm{t}|\, 0 < v(t) < 1\}$. Then, $W_1(t) = W_2(t) = 0$. Therefore,

$$v_i(t) = \frac{-\lambda_5}{\epsilon}.$$

2. Consider the set $\{\mathrm{t}|\, v(t) = 1\}$. Then, $W_1(t) = 0$. Then $W_2 \geq 0$. In other words,

$$v(t) + \frac{W_2}{\epsilon} = -\frac{\lambda_5}{\epsilon} > 1.$$

3. Consider the set $\{\mathrm{t}|\, v(t) = 0\}$. Then, $W_2(t) = 0$. Thus $W_1 \geq 0$. Consequently,

$$v(t) - \frac{W_i}{\epsilon} = -\frac{\lambda_5}{\epsilon} < 0.$$

Combining these cases, we can characterize the optimal control for $v^*(t)$ as

$$v^* = \min\left(\max\left(0, \frac{-\lambda_5}{\epsilon}\right), 1\right). \tag{20}$$

□

4 Numerical Simulations for Quadratic Control

A variation of the control strategy is given below.

We did a series of four different types of tests using Matlab's built in delay differential equation solver where we manually implemented the chemotherapy drugs for four days over a thirty day treatment cycle. The test types are as follows:

1. 4 days on the drug followed by 26 days off
2. 26 days off the drug followed by four days on
3. 13 days off, then 4 days on, ending with 13 days off
4. 4 days on, 22 days off, followed by 4 days on

The graphs for each type of test essentially behaved the same way. We have included above a graph of the fourth type of treatment describing the total tumor cell behavior. It is obvious that the overall treatment is not the most ideal case since the tumor cells are still growing at a high level, but there is some success in that the total tumor count was less with the drug than without the drug which is represented by the dashed line. The interesting part of the graph occurs in the beginning where there is an increase of overall tumor cells despite the fact that is when the chemotherapy drug is being given. We believe this behavior is possibly due to the delay in the model.

5 Conclusion

In conclusion, the successes of this paper include proving the existence and uniqueness of a solution, the existence of an optimal control, and a better understanding how to achieve better numerical results. After many trials and tribulations, we can safely say that more time and programming power is needed in order to effectively deal with the delay in this model. The numerical behavior included in this model match with the behavior of Lu *et. al* [9] which ensures us that future numerical work will be provide further insight.

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7 Appendix

In this section, we will give precise statements of the theorems used for proving the existence of a solution and existence of the optimal control.

Theorem 7.1 (R. D. Driver Continuity Condition [4])**.** *The Continuity Condition is satisfied if $F(t, x_t, y, z, I, u, v)$ is continuous with to t in $[0, t_f)$ for each given continuous function $\chi : [-\tau, t_f) \to \mathbb{R}$.*

optimal quadratic controls.

Theorem 7.2 (Das and Sharma Theorem [3])**.** *Formulation of an optimal control problem. Let $[0, t_f]$ be a fixed interval and S a domain on R^n. Let $\beta = (t \epsilon [0, t_f] BV([\alpha, t], S))$. We shall denote by $\mathbb{V}$ the set of all right continuous functions v of bounded variation on $[0, t_f]$ into a nonempty compact subset of Q of R^n.*

Consider a control process governed by the measure delay-differential equation $Dx = f(t, x_t, y, z, I, u, v(t))$ for $t > 0$

satisfying the following assumptions:

A_1: The functional f with range in R^n is defined for all $t \epsilon [0, t_f]$, for all $x \epsilon B$ and all $v \epsilon V$.

A_2: $f(t, x_t, y, z, I, u, v(t))$ is continuous in $t, x_t, y, z, I, u,$ and v.

A_3: There exists a Lebesgue integrable real function $r(t)$ for $t \epsilon [0, t_f]$ such that $|(f(t, x_t, y, z, I, u, v(t)| \leq r(t)$ uniformly with respect to $x \epsilon B$ and $v \epsilon V$

We are given the control problem with the following data:

$Dx = f(t, x_t, y, z, I, u, v(t)) \quad t \epsilon [0, t_f]$

with

1. *f satisfying the assumptions A_1 to A_3.*

2. *The fixed initial function $\phi \epsilon([\alpha, 0], S)$.*

3. *A target set T of nonempty compact sets $T_t \subset R^n$ defined on $[0, t_f]$ and upper semicontinuous with respect to inclusion;*

4. *The set V of admissable controls $v(t)$ defined on subintervals $[0, t_f]$ contained in $[0, t_f]$ with the same left endpoint (and perhaps different right endpoints $t_1 > t_0$) which transfer ϕ to T, which is such that for all $v \epsilon V$*

   $|(\Delta v)| \leqq \Delta h$

   on each subinterval of $[t_0, t_1]$, where h is a given nondecreasing right continuous function defined on $[0, t_f]$; (the symbol Δh on the interval, say, $[t_0, t_1]$ denotes $(h(t_1) - h(t_0))$;

5. *The cost functional*

   $J(v) = \int_0^{t_f} f^0(t, x(t), y(t), z(t), v(t))dt$

   where f^0 is a continuous real function defined on $[0, t_f] \times S \times Q$.

   Then if V is nonempty, there exists an optimal control in V.

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